Answer 1:

Bibliographic Information

A novel methionine aminopeptidase-2 inhibitor, PPI-2458, inhibits non-Hodgkin's lymphoma cell proliferation in vitro and in vivo. Cooper, Andrew C.; Karp, Russell M.; Clark, Edward J.; Taghizadeh, Nazbeh R.; Hoyt, Jennifer G.; Labenski, Matthew T.; Murray, Michael J.; Hannig, Gerhard; Westlin, William F.; Thompson, Charles D. Department of Cell Biology, Praecis, USA. Clinical Cancer Research (2006), 12(8), 2583-2590. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:347918 AN 2006:382700 CAPLUS

Abstract

Fumagillin and related compds. have potent antiproliferative activity through inhibition of methionine aminopeptidase-2 (MetAP-2). It has recently been reported that MetAP-2 is highly expressed in germinal center B cells and germinal center-derived non-Hodgkin's lymphomas (NHL), suggesting an important role for MetAP-2 in proliferating B cells. Therefore, we detd. the importance of MetAP-2 in normal and transformed germinal center B cells by evaluating the effects of MetAP-2 inhibition on the form and function of germinal centers and germinal center-derived NHL cells. To examine the activity of PPI-2458 on germinal center morphol., spleen sections from cynomolgus monkeys treated with oral PPI-2458 were analyzed. Antiproliferative activity of PPI-2458 was assessed on germinal center-derived NHL lines in culture. A MetAP-2 pharmacodynamic assay was used to det. cellular MetAP-2 inhibition following PPI-2458 treatment. Finally, inhibition of MetAP-2 and proliferation by PPI-2458 was examd. in the human SR NHL line in culture and in implanted xenografts. Oral PPI-2458 caused a redn. in germinal center size and no. in lymphoid tissues from treated animals. PPI-2458 potently inhibited growth (GI50 = 0.2-1.9 nmol/L) of several NHL lines in a manner that correlated with MetAP-2 inhibition. Moreover, orally administered PPI-2458 significantly inhibited SR tumor growth, which correlated with inhibition of tumor MetAP-2 (>85% at 100 mg/kg) in mice. These results show the potent antiproliferative activity of PPI-2458 on NHL lines in vitro and oral antitumor activity in vivo and suggest the therapeutic potential of PPI-2458 as a novel agent for treatment of NHL should be evaluated in the clin. setting.